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Study effects of DPP-4 inhibitors on liver function

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Abstract
D.M is chronic, metabolic disease characterized by elevated levels of blood glucose. There are many types of antidiabetic drugs such as insulin, biguanides, sulfonylurea, glinide, Thiazolidines, Glucose Sodium cotransporter2 inhibitors, a- glycoside inhibitors and DPP4 inhibitors.
Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, linagliptin) are a successful class of antidiabetic agents which improve glycaemic control with similar efficacy to other oral agents that acts on incretin hormones, mainly GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide) and associated with a low incidence of adverse events.
A comparative study of 58 patients were included in this study, including 48 diabetic patients and 10 non-diabetic patients. The diabetic patients were divided into three groups based on the type of DPP4 inhibitor they were taking.
All patients underwent liver function tests, including GPT, GOT, and ALP. Results showed that the ranges of liver function tests (GPT, GOT, and ALP) in diabetic patients taking DPP4 inhibitors (Sitagliptin, Vildagliptin, and Teneligliptin) were within the normal limits and were comparable to the liver function test results in non-diabetic patients.

Keywords: DPP4 inhibitors, Liver, ALP, GPT, GOT

Introduction
Diabetes is a heterogeneous group of syndromes characterized by elevated blood glucose attributed to a relative or absolute deficiency of insulin with disturbances of carbohydrate, fat, and protein metabolism [1, 2].

Dipeptidyl peptidase-4 Inhibitors
Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, Teneligliptin) are a successful class of antidiabetic agents which improve glycaemic control with similar efficacy to other oral agents, but without many of the adverse effects of other therapies [3]. GLP-1 is a gut hormone released in response to digestion and absorption of food in the small intestine, which is responsible for an important part of postprandial insulin secretion [4].

- **Pharmacokinetics**

Absorption: A study of oral and IV administration of sitagliptin in healthy volunteers demonstrated 87% bioavailability of the oral dose [5].

Distribution: The distribution of sitagliptin and sitagliptin generally depends on a variety of factors, such as plasma protein binding. Both drugs demonstrate low binding to proteins in the serum [6, 7].

Metabolism: Metabolism is mediated primarily by the cytochrome P450 (3A4/5) system [6].

Excretion: Renal and hepatic pathways are involved in the elimination of oral doses of these agent [7].

- **Mechanism of Action**

They act on incretin hormones, mainly GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide), which maintain glucose homeostasis by increasing insulin secretion and decreasing glucagon secretion [8]. GLP-1 is a hormone secreted by enteroendocrine L cells of the small intestine, which lowers blood glucose by stimulating insulin secretion, reducing glucagon concentrations, and delaying gastric emptying [9]. It has a half-life of fewer than 2 minutes [10]. GIP is a hormone secreted in the stomach and proximal small intestine by neuroendocrine K-cells. Its half-life is approximately 7 minutes in healthy individuals and 5 minutes in individuals with type 2 diabetes [10] .
These incretins are released within minutes of food intake, and DPP-4 degrades these hormones immediately due to their short half-life. By inhibiting the DPP-4 enzyme, DPP-4 inhibitors increase the levels of GLP-1 and GIP, which in turn increase beta cell insulin secretion in the pancreas, thereby reducing postprandial and fasting hyperglycaemia [8].

- **Adverse Effects**

Gliptins are associated with a low incidence of adverse events, including hypoglycaemia, and have weight neutral effects [11].
The most common side effects noticed with the DPP-4 inhibitors sitagliptin and sitagliptin are upper respiratory tract infection, nasopharyngitis, headache, urinary tract infection, arthralgia [9]. Sitagliptin was also associated with Stevens-Johnson syndrome in post marketing reports [9]. Reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotizing variants, have correlations with the use of sitagliptin, vildagliptin, and sax gliptin in post marketing data [12].

- **Contraindications**

Contraindications to gliptins include type 1 diabetes and diabetic ketoacidosis.

- **Toxicity**

High doses of sitagliptin were associated with an 8.0-millisecond mean increase in QTc in controlled clinical trials as labelled by the FDA. In case of overdose, haemodialysis removes approximately 13% of sitagliptin and approximately 23% of sax gliptin but did not affect AL gliptin or linagliptin. [13]

Patients and Methods

A total of 58 patients were included in this study, including 48 diabetic patients and 10 non-diabetic patients. The diabetic patients were divided into three groups based on the type of DPP4 inhibitor they were taking: 42 patients were taking Sitagliptin, 3 patients were taking Teneligliptin, and 3 patients were taking Vildagliptin. The ages of the diabetic patients ranged from 43 to 75 years. Of the 42 diabetic patients, 30 were females and 18 were males. The non-diabetic patients included 5 females and 6 males, with ages ranging from 38 to 62 years.

All patients underwent liver function tests, including GPT, GOT, and ALP. The liver function test results were collected from medical records. For the diabetic patients, the liver function test results were collected during routine follow-up visits after starting DPP4 inhibitor therapy. For the non-diabetic patients, the liver function test results were collected during routine health check-ups.

The liver function tests were performed using standard laboratory procedures. GPT, GOT, and ALP levels were measured in serum samples using an automated analyser. The normal ranges for GPT, GOT, and ALP were 5-40 U/L, 5-40 U/L, and 35-105 U/L, respectively.

All Data was collected at Al-Mahaweli General hospital from 10th of November to 15th of January according to table below:

Table 1: Liver Function Test in Different Patient With D.M Type2

Patient name	Age	Gander	Sitagliptin	Ten gliptin	Vildagliptin	G.P.T	G.O.T	ALP

Results

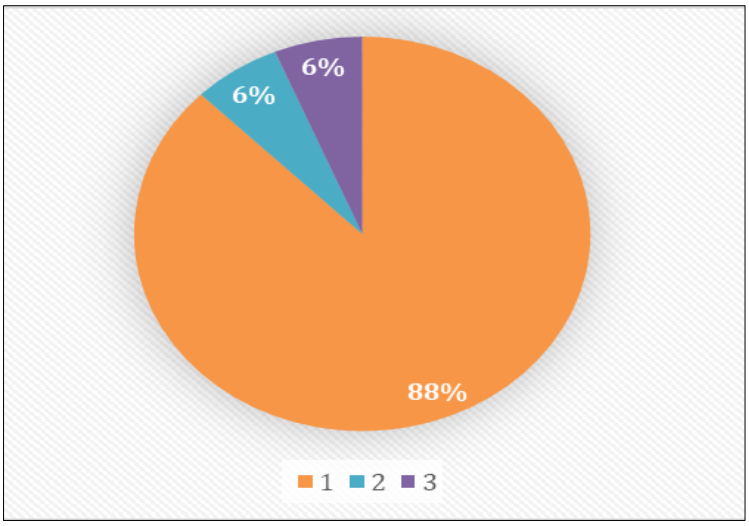

Fig 1: Predominant use of dpp4 inhibitors. green colour: sitagliptin, blue colour: vildagliptin and yellow colour: teneligliptin.

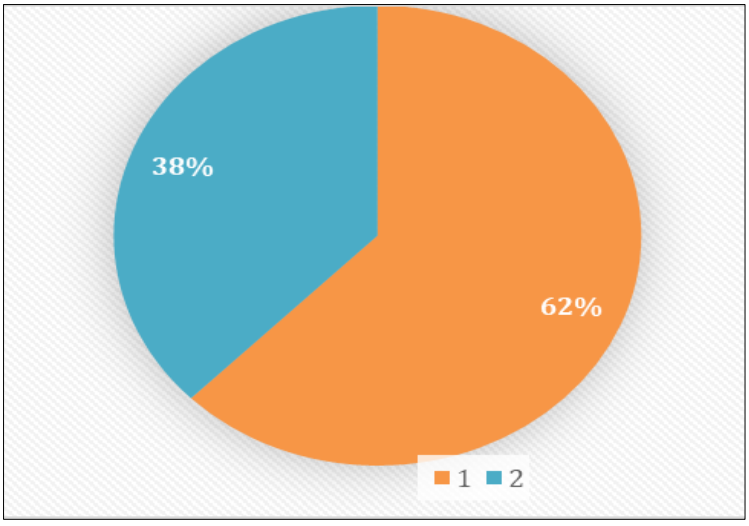

Fig 2: Female to male diabetic Patients ratio. green colour: female patients and blue colour: male patients

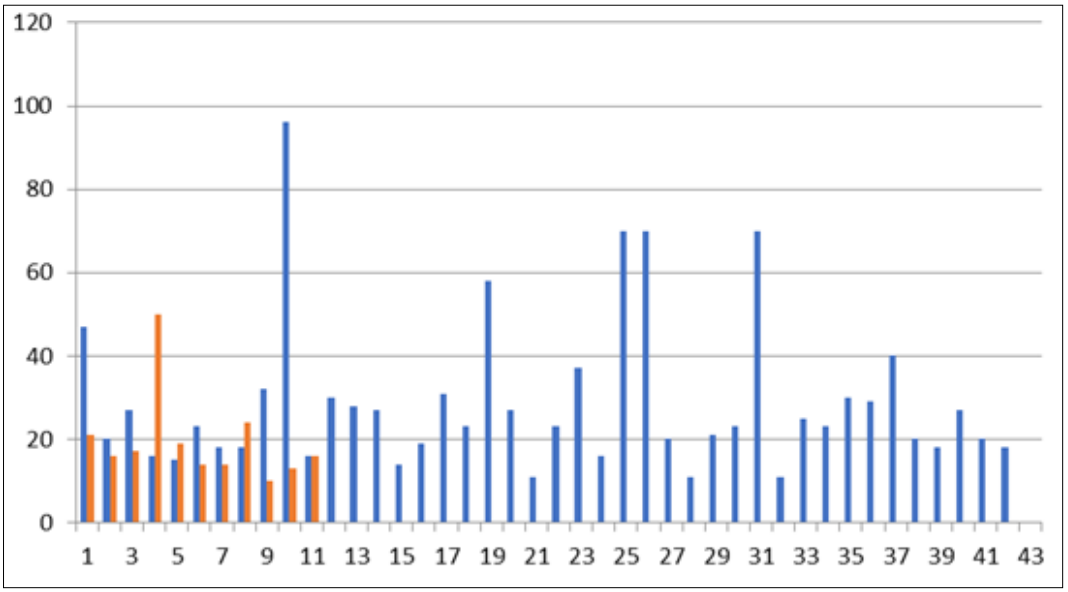

Fig 3: Sitagliptin effect on gpt. blue color: Patients group, orange color: Control group

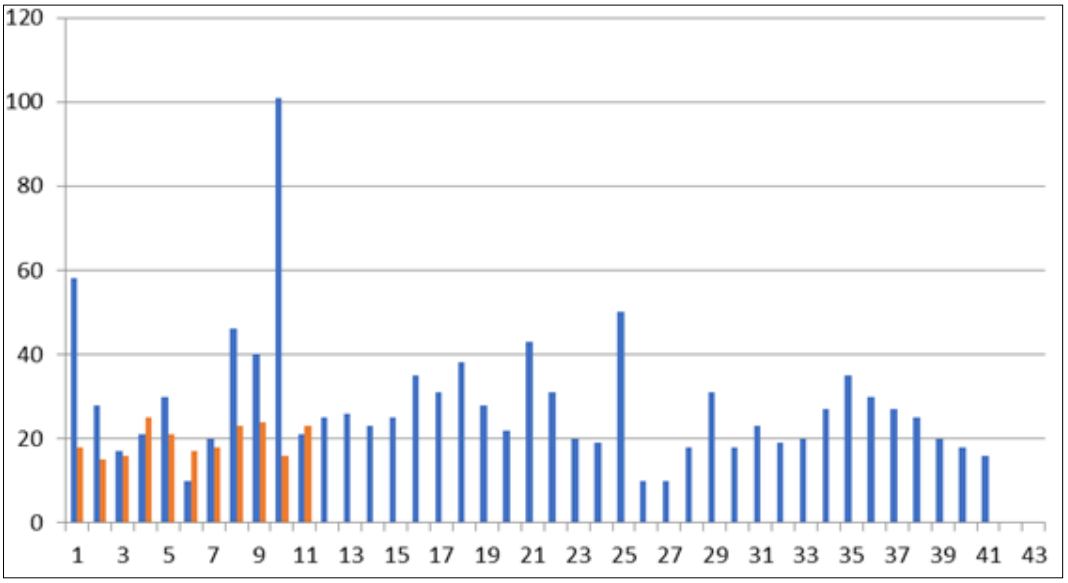

Fig 4: Sitagliptin effect on Got. blue color: Patients group, orange color: control group

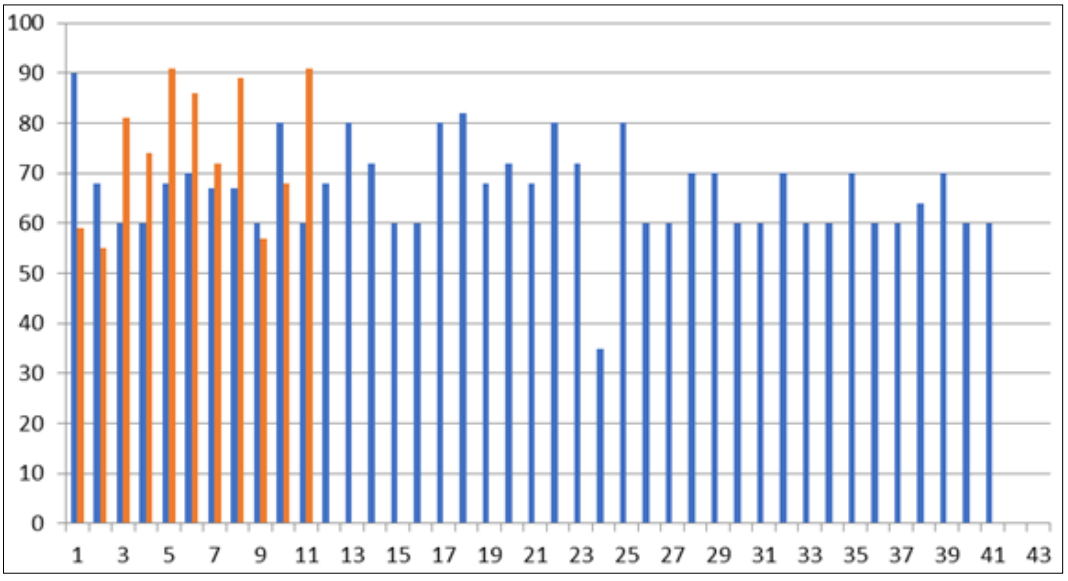

Fig 5: Sitagliptin effect on alp. blue color: Patients group, orange color: control group

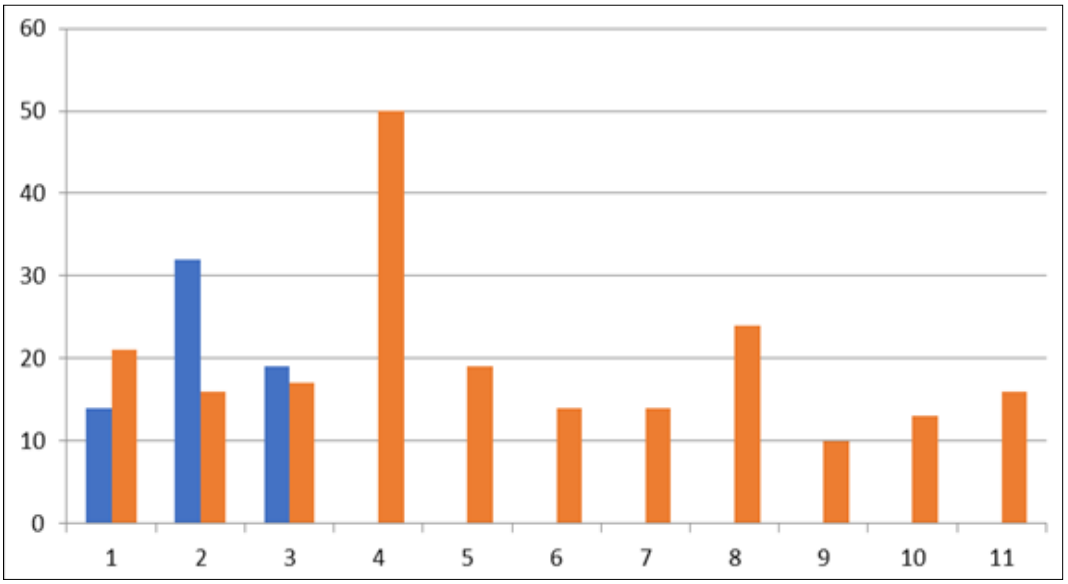

Fig 6: Vildagliptin effect on gpt. blue color: Patients group, orange color: control group

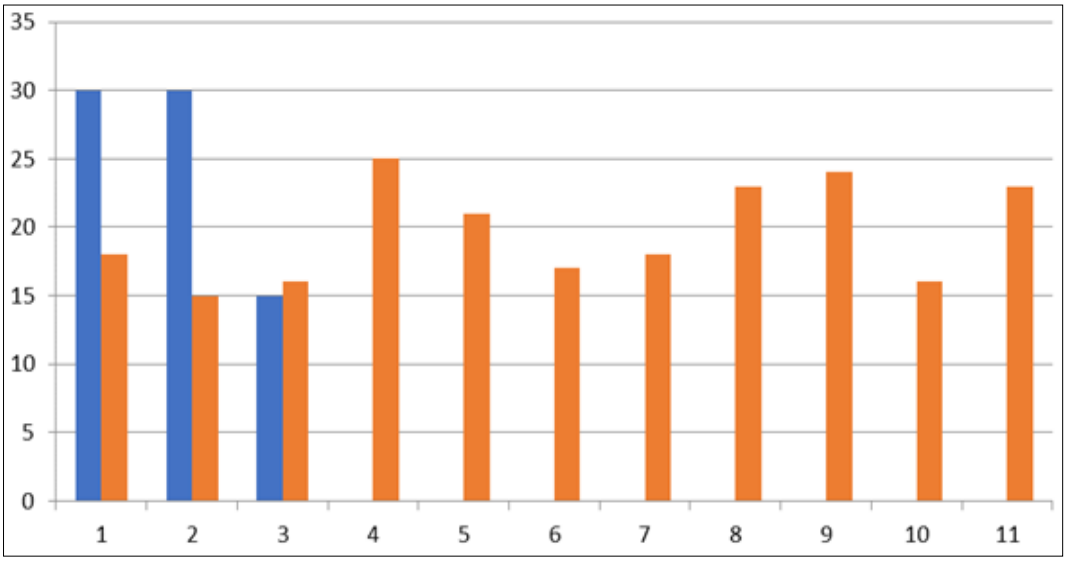

Fig 7: Vildagliptin effect on got. blue color: Patients group, orange color: control group

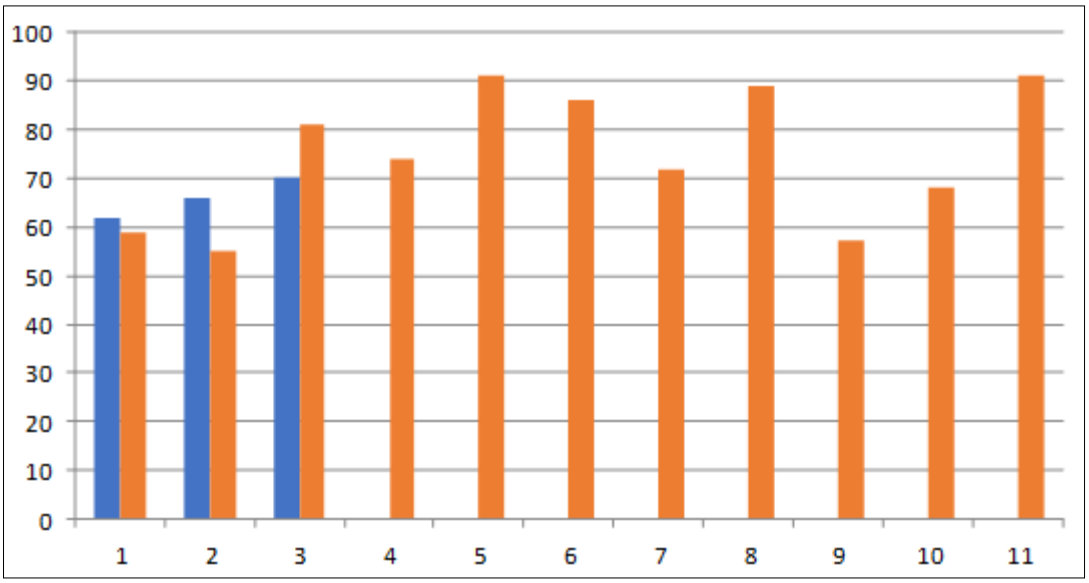

Fig 8: Vildagliptin effect on Alp. blue color: Patients group, orange color: control group

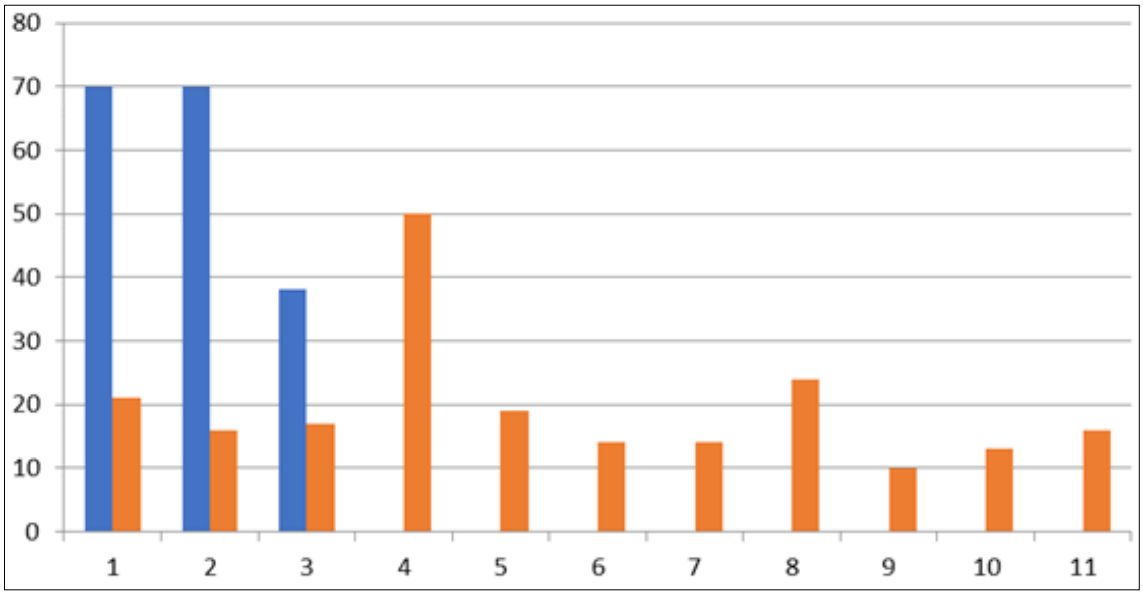

Fig 9: Teneligliptin effect on Gpt. blue color: Patients group, orange color: control group

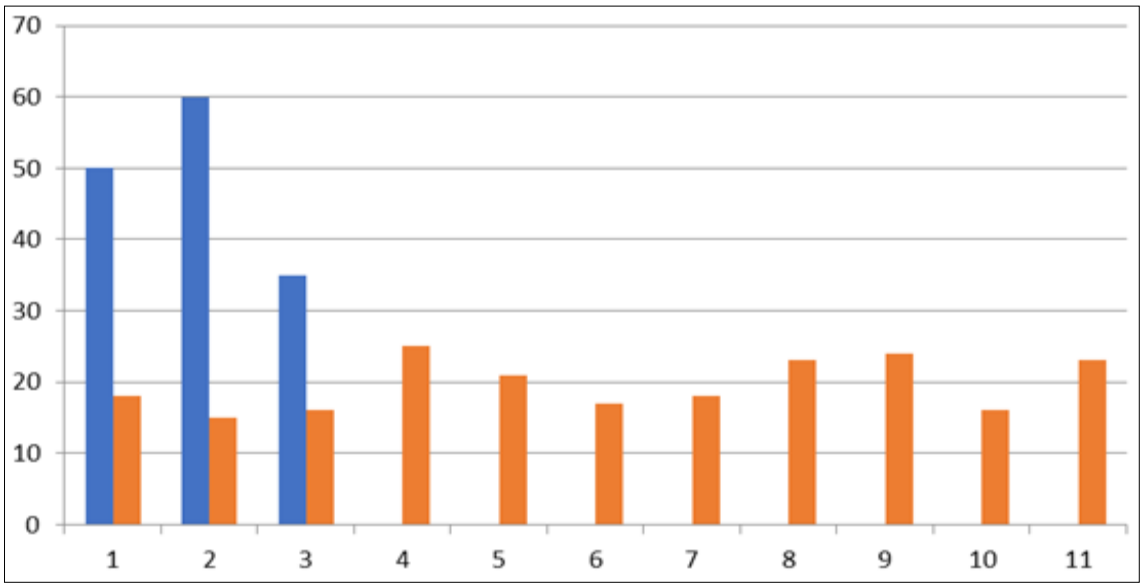

Fig 10: Teneligliptin effect on got. blue color: Patients group, orange color: control group

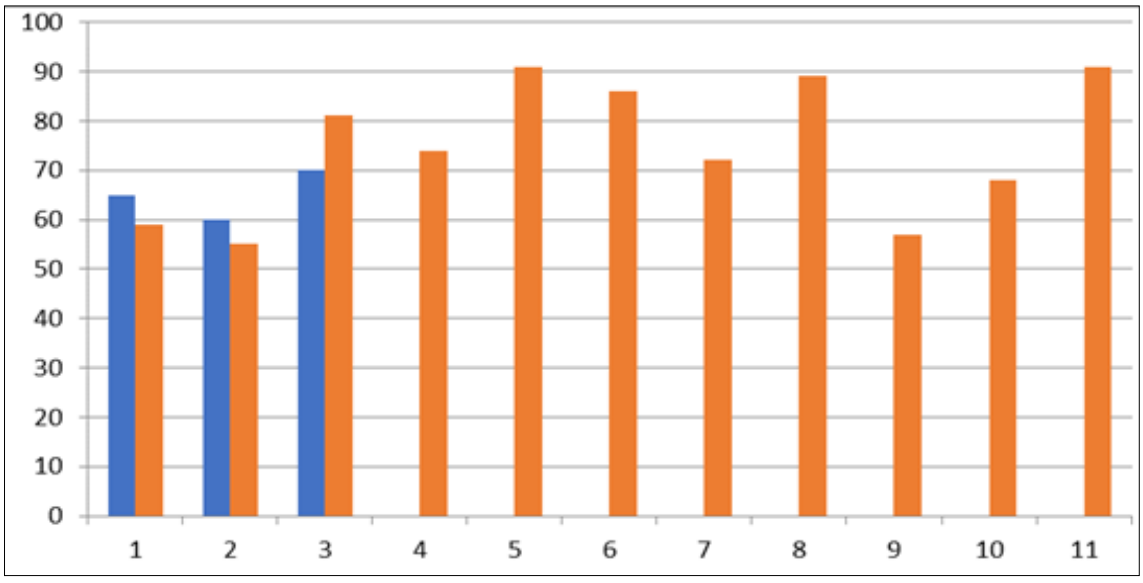

Fig 11: Teneligliptin effect on alp. blue color: Patients group, orange color: control group

Discussion

Based on the data we've been collected and analysed, we found that the ranges of liver function tests (GPT, GOT, and ALP) in diabetic patients taking DPP4 inhibitors (Sitagliptin, Vildagliptin, and Teneligliptin) were within the normal limits and were comparable to the liver function test results in non-diabetic patients. These findings suggest that DPP4 inhibitors have a minimal or no adverse effect on liver function in diabetic patients.

These results are consistent with previous research in this area (DPP-4 Inhibitors Improve Liver Dysfunction in Type 2 Diabetes Mellitus). The clinical research we found, for example, supports our findings that DPP4 inhibitors can improve liver function in patients with type 2 diabetes and liver dysfunction. This is important because many patients with diabetes also have liver dysfunction, and the medications they take for their diabetes can sometimes exacerbate liver problems like (Metformin and Sulfonylureas) [14]

However, it is important to note that our study has some limitations, such as the small sample size and longer follow-up period. These limitations suggest the need for further research in this area with larger sample sizes However, further research with larger sample sizes and longer follow-up periods may be needed to confirm these findings and to assess the long-term effects of these medications on liver function. Also to better understand the effect of DPP4 inhibitors on liver function in diabetic patients.

In conclusion, our study provides valuable information about the effect of DPP4 inhibitors on liver function tests in diabetic patients. our findings suggest that DPP4 inhibitors have minimal or no adverse effect on liver function in diabetic patients. This information is important for clinicians and patients who are concerned about the potential adverse effects of diabetes medications on liver function.

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